

# Relationship Between B-Type Natriuretic Peptides and Pulmonary Capillary Wedge Pressure in the Intensive Care Unit

Paul R. Forfia, MD, Stanley P. Watkins, MD, J. Eduardo Rame, MD, Kerry J. Stewart, EdD, Edward P. Shapiro, MD  
*Baltimore, Maryland*

<b>OBJECTIVES</b>	We examined whether B-type natriuretic peptides (BNP) can serve as noninvasive markers of pulmonary capillary wedge pressure (PCWP) in the setting of critical illness.
<b>BACKGROUND</b>	The BNP and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are highly correlated with left ventricular (LV) filling pressures in patients with depressed LV systolic function. However, their relationship to PCWP in a heterogeneous intensive care unit (ICU) population has not been established.
<b>METHODS</b>	We prospectively studied 40 patients in the ICU requiring invasive hemodynamic monitoring. Hemodynamics were recorded simultaneously with blood sampling for BNP and NT-proBNP.
<b>RESULTS</b>	The BNP (median 420 pg/ml) and NT-proBNP (median 3,304 pg/ml) levels were markedly elevated, but weakly correlated with PCWP (BNP, $r = 0.40$ , NT-proBNP, $r = 0.32$ ) and other cardiac parameters. Peptide levels were approximately four-fold greater in patients with impaired (estimated glomerular filtration rate [eGFR] $<60$ ml/min) versus normal (eGFR $>60$ ml/min) renal function, despite similar PCWP, cardiac index, and LV ejection fraction. In addition, both BNP and NT-proBNP showed stronger correlations with PCWP in patients with preserved (BNP, $r = 0.58$ , NT-proBNP, $r = 0.73$ ) versus impaired renal function (BNP, $r = 0.48$ , NT-proBNP, $r = 0.34$ ). Interaction terms between eGFR and BNP ( $p = 0.06$ ) and NT-proBNP ( $p = 0.04$ ) suggest that eGFR modulates the relationship of these peptides to filling pressures.
<b>CONCLUSIONS</b>	The BNPs are markedly elevated, yet show only weak correlations to PCWP in ICU patients requiring invasive hemodynamic monitoring. Thus, a single value for BNP or NT-proBNP may not be a clinically useful noninvasive marker of filling pressures in the critically ill patient. This appears to be especially true in patients with impaired renal function. (J Am Coll Cardiol 2005;45:1667-71) © 2005 by the American College of Cardiology Foundation

The B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are co-secreted from the cardiac ventricles in response to stretch and other non-mechanical stimuli (1,2). Both peptides are markers of left ventricular (LV) dysfunction, and elevated levels aid in discriminating cardiac from non-cardiac dyspnea (3). Peptide levels also correlate with LV filling pressures in patients with depressed systolic function (4,5). However, it is unclear whether BNP or NT-proBNP are markers of pulmonary capillary wedge pressure (PCWP) in a population of critically ill patients with a broad range of diagnoses and cardiac function.

We conducted a prospective observational study examining the relationship between BNP and NT-proBNP and PCWP in critically ill patients requiring invasive hemodynamic monitoring. We sought to determine whether these peptides can be used as noninvasive markers of pulmonary congestion in this cohort.

## METHODS

**Study population.** Adult intensive care units (ICUs) were screened for patients in whom a pulmonary artery catheter

(PAC) had been inserted for a clinical indication. Patients with an acute myocardial infarction, a troponin I level  $>1.0$  ng/ml, and those recovering from cardiac surgery or receiving nesiritide were excluded. Informed consent was obtained. The study was approved by the Johns Hopkins Institutional Review Board.

**Hemodynamics.** Adequate position of the PAC was confirmed by radiograph and hemodynamic waveform analysis. All PAC-derived hemodynamics were recorded at end expiration, with PCWP adjusted for a positive end expiratory pressure  $\geq 10$  cm H<sub>2</sub>O (6). Cardiac output was measured by thermodilution in triplicate. An echocardiogram was performed the same day as the study. Left ventricular dimensions, mass, wall stress, and left ventricular ejection fraction (LVEF) were measured as previously described (7).

Glomerular filtration rate was estimated using the method of Cockcroft and Gault, incorporating ideal body weight (8). An estimated glomerular filtration rate (eGFR)  $<60$  ml/min defined impaired renal function (9).

**Blood sampling.** Arterial blood was collected simultaneously with hemodynamic recordings and analyzed within 1 h. The BNP analysis was performed on whole blood using the Triage BNP assay (Biosite Inc., San Diego, California) (3). The NT-proBNP analysis was performed on serum using a standard core laboratory assay (Roche Diagnostics, Basel,

From the Division of Cardiology, Johns Hopkins Hospital, Baltimore, Maryland.  
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#### Abbreviations and Acronyms

BNP	= B-type natriuretic peptide
CI	= cardiac index
eGFR	= estimated glomerular filtration rate
ICU	= intensive care unit
IQR	= interquartile range
LV	= left ventricular
LVEF	= left ventricular ejection fraction
NT-proBNP	= N-terminal pro-B-type natriuretic peptide
PAC	= pulmonary artery catheter
PCWP	= pulmonary capillary wedge pressure

Switzerland). Values above the upper limit of the BNP and NT-proBNP assays were reported as 5,000 and 70,000 pg/ml, respectively. Samples run in duplicate ( $n = 7$ ) varied by 1%, with a correlation coefficient of 0.99.

**Statistical analysis.** Values are expressed as the median and interquartile range (IQR). Differences between medians were detected by Wilcoxon rank-sum test with two-tailed  $p$  values of  $<0.05$ . Because the natriuretic peptide data were not normally distributed, log BNP and log NT-proBNP were used in the correlations and regression models. A multivariate linear regression model was used to ascertain independent predictors of BNP and NT-proBNP. The interaction between BNP (and NT-proBNP) and eGFR on the relationship to PCWP was tested in a regression model. An interaction term was created by entering log BNP (and log NT-proBNP) into the model as a continuous variable and eGFR as a binary variable, defined as normal (GFR  $>60$  ml/min) or abnormal (GFR  $<60$  ml/min). A  $p$  value  $<0.05$  was considered significant. Statistical analyses were performed using Stata software version 8.0 (College Station, Texas).

## RESULTS

**Population characteristics.** Table 1 summarizes the baseline clinical characteristics and hemodynamics of this critically ill population. The median age was 62 years. Approximately two-thirds of patients were intubated and mechanically ventilated. A similar proportion of patients had renal insufficiency (75% acute, 25% chronic). The majority of patients (68%) had preserved LV systolic function (LVEF  $\geq 50\%$ ). Fourteen patients (35%) died while in the hospital.

**BNPs and hemodynamics.** The concentrations of BNP (median 420 pg/ml, IQR 197 to 1,740) and NT-proBNP (median 3,304 pg/ml, IQR 1,153 to 14,713) were markedly elevated. However, natriuretic peptide levels showed only weak correlations with PCWP (Fig. 1). Inspection of each scatterplot revealed wide variations in PCWP for any given value of BNP and NT-proBNP. Both peptides also showed weak but significant correlations with other central hemodynamic parameters, troponin levels, and inverse correlations with LVEF and eGFR (Table 2). After adjusting for

**Table 1.** Clinical Characteristics and Hemodynamics of the 40 Patients

Clinical characteristics	
Demographics	
Age, yrs (median; IQR)	62 (52; 73)
Men	22 (55)
Women	18 (45)
White	28 (70)
Black	10 (25)
Other	2 (5)
Unit	
Cardiac intensive care unit	17 (43)
Surgical intensive care unit	23 (57)
Diagnosis	
Congestive heart failure	12 (30)
Sepsis or ARDS	12 (30)
Major abdominal surgery	9 (23)
Major vascular surgery	4 (10)
Trauma	3 (8)
Intubated/mechanically ventilated	26 (65)
Pressors/inotropes	15 (38)
Intra-aortic balloon pump	2 (5)
Hemodynamic parameters	
Heart rate, beats/min	83 (76, 108)
RAP, mm Hg	10 (8, 13)
Mean PAP, mm Hg	29 (21, 35)
PCWP, mm Hg	14 (10, 22)
CO, l/min	5.9 (4, 8.3)
CI, l/min/m <sup>2</sup>	3.1 (2.1, 4.2)
SV, ml/beat	73 (48, 93)
Systemic vascular resistance, dyne $\cdot$ sec $\cdot$ cm <sup>5</sup>	923 (723, 1,635)
Ejection fraction, %	50 (20, 60)

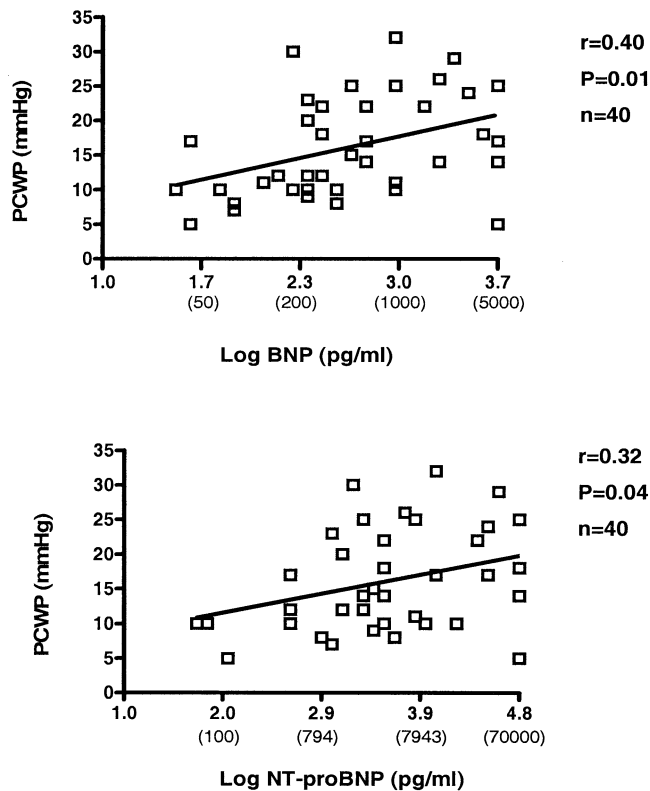
Clinical characteristic data are expressed as number of patients (%). Hemodynamic data expressed as median (interquartile range).

ARDS = acute respiratory distress syndrome; CI = cardiac index; CO = carbon monoxide; IQR = interquartile range; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; SV = stroke volume.

PCWP and LVEF, eGFR remained a significant independent predictor of both BNP (beta coefficient  $-0.45$ ,  $p = 0.002$ ) and NT-proBNP (beta coefficient  $-0.56$ ,  $p = 0.001$ ). Body mass index, vasopressors, mechanical ventilation, and hypoxemia ( $PO_2/FiO_2$  ratio) did not affect natriuretic peptide levels (data not shown).

Figure 2 demonstrates that natriuretic peptide levels were approximately four-fold higher in patients with impaired versus normal renal function, despite no differences in PCWP, cardiac index (CI), or LVEF. In addition, mean wall stress did not differ between the two groups (GFR  $>60$  ml/min, 181 g/cm<sup>2</sup> vs. GFR  $<60$  ml/min, 175 g/cm<sup>2</sup>;  $p = 0.20$ ).

Figure 3 displays the correlations of BNP and NT-proBNP to PCWP in the patients with normal and impaired renal function. For both peptides, the slope of the regression lines increased, and the univariate correlations with PCWP strengthened in patients with an eGFR  $>60$  ml/min versus an eGFR  $<60$  ml/min. A similar trend was seen in the correlations between the natriuretic peptide and pulmonary artery pressure, CI, and LVEF when stratified by renal function (Table 3). The interaction term for BNP ( $p = 0.06$ ) strongly suggests, and for NT-proBNP ( $p =$



**Figure 1.** Scatterplots showing the correlation between pulmonary capillary wedge pressure (PCWP) and log B-type natriuretic peptide (BNP) (top) and log N-terminal pro-B-type natriuretic peptide (NT-proBNP) (bottom) in the overall cohort. Values in parentheses indicate raw BNP and NT-proBNP values.

0.04), confirms, that renal function modulates the strength of the relationship between the natriuretic peptides and PCWP.

## DISCUSSION

The present study demonstrates that natriuretic peptide levels were markedly elevated, but weakly correlated with invasive hemodynamics, most notably PCWP, in the setting of critical illness. Regression analysis revealed that the PCWP varied widely at any given BNP and NT-proBNP concentration. Moreover, circulating concentrations of BNP and NT-proBNP were profoundly influenced by the presence of renal failure, independent of pulmonary congestion or depressed cardiac function. Thus, evidence from the current study suggests that neither BNP nor NT-proBNP are reliable markers of pulmonary congestion in critically ill patients.

**BNPs and hemodynamics.** The relatively weak correlations between BNP and NT-proBNP and PCWP in the current study are at odds with previous studies showing strong correlations between these peptides and LV filling pressures (4,5). However, in contrast to the current study, previous studies have focused almost exclusively on patients with significant LV systolic dysfunction. This is an important distinction, as BNP release occurs as a direct result of

cardiac stretch, not pressure, and thus is more closely coupled to hemodynamics in the failing versus non-failing heart (4,10–12). In addition, previous studies have excluded critically ill patients, thus minimizing the contributions of potentially important non-mechanical stimuli for BNP release, such as neurohormonal activation and myocardial ischemia, both of which occur commonly in the setting of critical illness (13,14). Consistent with our results, a recent study showed that BNP levels weakly correlated with PCWP ( $r = 0.32$ ,  $p = 0.02$ ) in a mixed ICU cohort, with the optimal cutoff for BNP <60% specific for a PCWP >15 mm Hg (15).

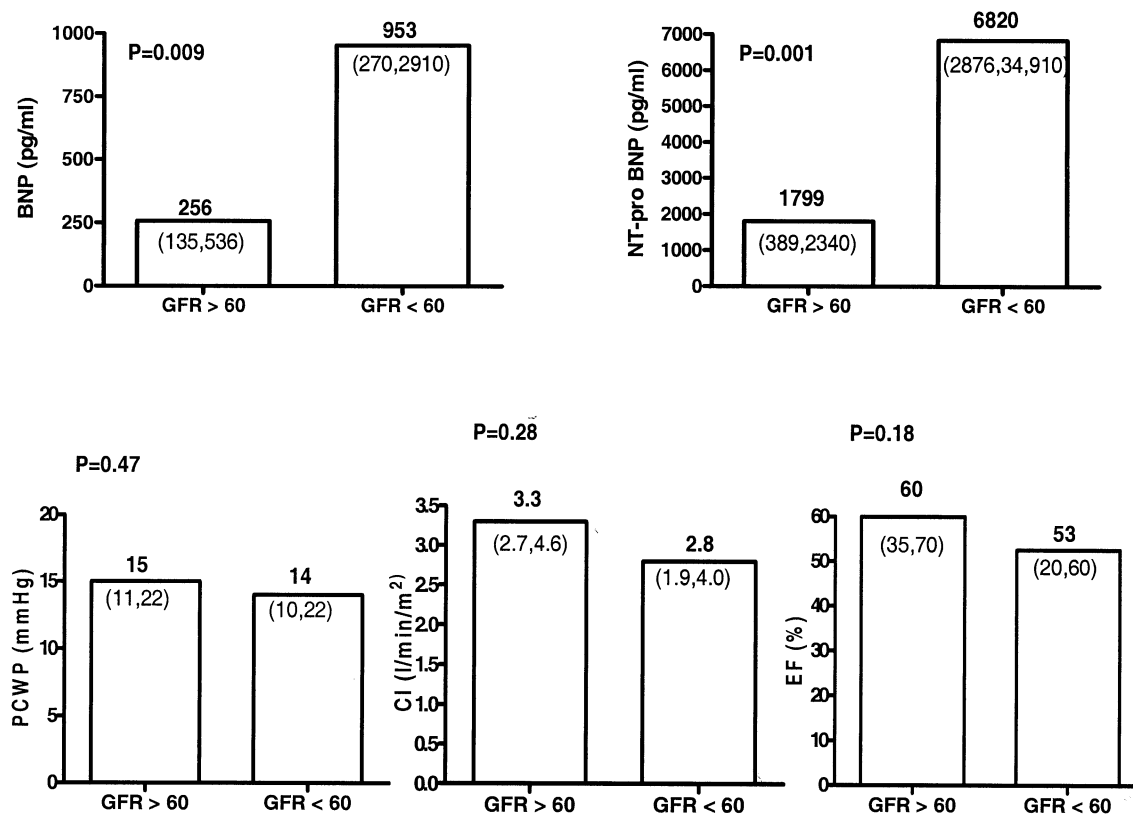
**BNPs and renal function.** Previous studies have shown that natriuretic peptide levels correlate inversely with GFR in chronic kidney disease (16,17). Investigators have postulated that higher filling pressures and wall stress play an important role in this cardiorenal link. However, in our patients with renal failure (75% acute), natriuretic peptide levels were massively elevated and could not be explained on the basis of higher filling pressures, wall stress, or depressed cardiac function. Moreover, natriuretic peptide levels >1,000 pg/ml (BNP) and 10,000 pg/ml (NT-proBNP) were more specific for a GFR <60 (BNP, 92%; NT-proBNP, 100%) than for a PCWP >18 mm Hg (BNP, 42%; NT-proBNP, 60%).

To our knowledge, this study is the first to document such natriuretic peptide-hemodynamic dissociations in the setting of renal failure and suggests that renal function has a more direct effect on circulating natriuretic peptide levels than previously recognized. Moreover, the present study highlights the important limitations of these peptides as hemodynamic markers in this context. Further study is warranted to determine what factors account for the increased natriuretic peptide levels in renal failure (i.e., neu-

**Table 2.** Univariate Correlations ( $r$ ) of Log BNP and Log NT-proBNP With Hemodynamic and Other Parameters in the Overall Cohort ( $n = 40$ )

Variable	BNP		NT-proBNP	
	$r$	p Value	$r$	p Value
RAP	0.21	0.20	0.23	0.15
mPAP	0.42	0.008	0.38	0.02
PCWP	0.40	0.01	0.32	0.04
CI	−0.37	0.02	−0.33	0.04
EF	−0.49	0.002	−0.36	0.03
GFR	−0.35	0.03	−0.45	0.004
Age	0.21	0.19	0.22	0.18
Troponin I	0.33	0.04	0.43	0.006
LV mass	0.31	0.10	0.13	0.52
LVIDd	0.15	0.47	0.04	0.82
LVIDs	0.23	0.26	0.13	0.50

BNP = B-type natriuretic peptide; EF = ejection fraction; GFR = glomerular filtration rate; LV = left ventricular; LVIDd = left ventricular diastolic diameter; LVIDs = left ventricular systolic diameter; mPAP = mean pulmonary artery pressure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; other abbreviations as in Table 1.

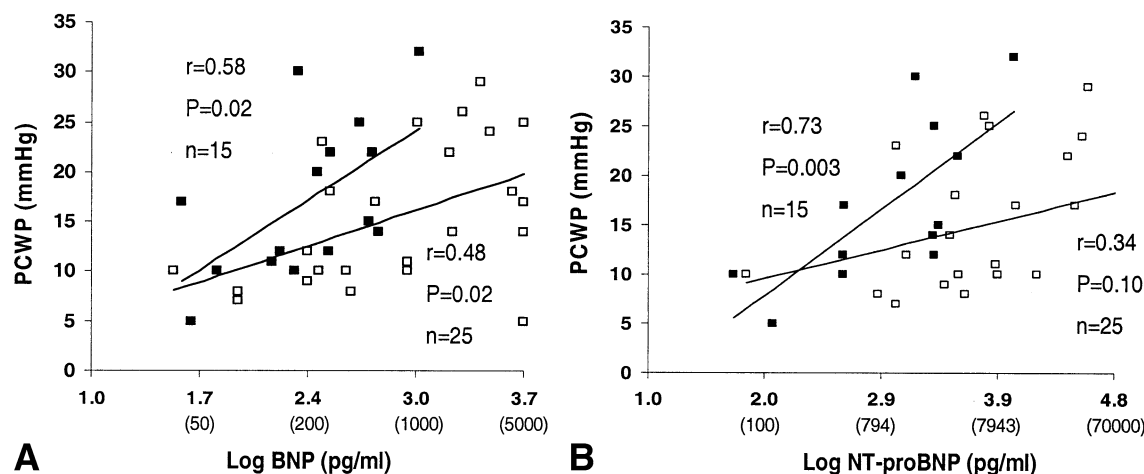


**Figure 2.** Bar graphs showing B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) values (**top**), and pulmonary capillary wedge pressure (PCWP), cardiac index (CI), and ejection fraction (EF) (**bottom**) in patients with an estimated glomerular filtration rate (eGFR) >60 ml/min and an eGFR <60 ml/min. Median values are shown in **bold**, with interquartile ranges shown in **parentheses**.

rohormonal activation vs. impaired clearance), as well as the significance of acute versus chronic kidney disease in this paradigm.

**Study limitations.** The relatively small sample size in our study limited our ability to make more definitive conclusions about associations between the natriuretic peptide and hemodynamics and the modifying role of renal function. This likely explains why the interaction term for BNP and

eGFR fell just short of statistical significance in the PCWP regression, despite evidence that renal function affects the circulating levels and the hemodynamic associations of both peptides. A potential methodologic limitation was the use of the Cockcroft-Gault formula to estimate GFR, as opposed to the Modification of Diet in Renal Disease formula for estimation of GFR (13). However, eGFRs derived from both formulas were highly correlated in our dataset ( $r =$



**Figure 3.** Scatterplots showing the correlation between pulmonary capillary wedge pressure (PCWP) and log B-type natriuretic peptide (BNP) (A) and log N-terminal pro-B-type natriuretic peptide (NT-proBNP) (B) in patients with an estimated glomerular filtration rate (eGFR) >60 ml/min (**closed squares**) and an eGFR <60 ml/min (**open squares**).

**Table 3.** Univariate Correlations (r) for Log BNP and Log NT-proBNP in Patients With eGFR >60 ml/min (n = 15) and <60 ml/min (n = 25)

Variable	BNP		NT-proBNP	
	r; p Value	r; p Value	r; p Value	r; p Value
	GFR >60	GFR <60	GFR >60	GFR <60
RAP	0.40; 0.14	0.31; 0.13	0.56; 0.04	0.28; 0.16
mPAP	0.54; 0.04	0.50; 0.01	0.66; 0.01	0.43; 0.03
PCWP	0.58; 0.02	0.48; 0.02	0.73; 0.003	0.34; 0.10
CI	-0.62; 0.01	-0.32; 0.13	-0.71; 0.004	-0.23; 0.27
EF	-0.58; 0.02	-0.43; 0.04	-0.60; 0.03	-0.21; 0.32

eGFR = estimated glomerular filtration rate; other abbreviations as in Tables 1 and 2.

0.86), and analyses using the MDRD formula did not alter our results.

**Clinical implications.** The present study indicates that in the setting of critical illness, BNP and NT-proBNP are not reliable markers of circulatory congestion. This was especially true in patients with impaired renal function, as 75% to 80% of the patients with a GFR <60 ml/min would have been inappropriately diuresed if standard cutoffs for BNP and NT-proBNP had been used to indicate pulmonary congestion. Thus, physicians should exercise caution in how they interpret elevated peptide concentrations in the ICU setting, particularly in patients with renal failure.

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**Reprint requests and correspondence:** Dr. Edward P. Shapiro, Johns Hopkins Bayview Medical Center, 4940 Eastern Avenue, Baltimore, Maryland 21224. E-mail: eshapiro@jhmi.edu.

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